"BURST-FREE" SUSTAINED RELEASE POLY-(LACTIDE/GLYCOLIDE) MICROSPHERES

CROSS REFERENCE

This application is a continuation application of U.S. patent application Ser. No. 08/590,973, filed Jan. 24, 1996 now abandoned, which is a continuation-in-part of U.S. patent application Ser. No. 08/446,149, filed May 22, 1995 now abandoned.

GOVERNMENT INTERESTS

The invention described herein may be manufactured, licensed and used by or for governmental purposes without the payment of any royalties to us thereon.

FIELD OF THE INVENTION

This invention relates to providing novel biocompatible and biodegradable microspheres for burst-free programmable sustained release of biologically active agents, inclusive of polypeptides, over a period of up to 100 days in an aqueous physiological environment.

BACKGROUND OF THE INVENTION

Several publications and patents are available for sustained release of active agents from biodegradable polymers, particularly, poly(lactide/glycolides) (PLGA). Prior usages of PLGA for controlled release of polypeptides have involved the use of molar ratios of lactide/glycolide (L/G) of 75/25 to 100/0 for molecular weights >20,000. Further prior art preparations of PLGA utilized fillers or additives in the inner aqueous layer to improve the stability and encapsulation efficency and/or to increase the viscosity of the aqueous layer, thereby modulating polymer hydrolysis and the biologically active agent or polypeptide release.

In addition, the prior art use of PLGA copolymers were end-capped, in that the terminal carboxyl end groups were blocked. In these end-capped co-polymers, the microcapsule preparations exhibited a low to moderate burst release of ~10–40% of the entrapped polypeptide in the first 24 hours after placement in an aqueous physiological environment. In part, these characteristics are due to the use of fillers in the inner aqueous phase. Further, a 1-month release of polypeptide is known with the use of a 75/25 co-polymer of PLGA of Mw <20,000.

Investigations in controlled release research has been proceeding especially to obtain a 1 to 2 month delivery system for biologically active agents or polypeptides using poly(lactide/glycolide) polymers. However, most of these systems have one or more of the following problems: Poor encapsulation efficency and large 'burst release' followed by an intermediate 'no release' or 'lag phase' until the polymer degrades. In general, release from these polymers occur over a period from about 4 weeks to about several months. In addition, in order to achieve this release a 50/50 copolymer of MW >30,000 or a 75/25 copolymer of Mw >10,000 are employed which often results in residual polymer remaining at the site of administration long after the release of active core.

SUMMARY OF THE INVENTION

This invention provides biocompatible and biodegradable microspheres that have been designed for novel, burst free, programmable sustained release of biologically active agents, including polypeptides over a period of up to 100 days in an aqueous physiological environment.

Unlike currently available release systems, which rely on the use of fillers/additives such as gelatin, albumin, dextran, pectin, polyvinyl pyrrolidone, polyethylene glycol, sugars, etc., and are still prone to low encapsulation efficiencies and "burst effects", this invention achieves high encapsulation and "burst-free" release without the use of any additive. In this invention, burst-free, programmable sustained release is achieved through the use of a unique blend of the 'uncapped' and end-capped forms of poly(lactide/glycolide) polymer in the molecular weight range of 2,000 to 60,000 daltons.

In general, microspheres described in this invention are produced by a unique emulsification technique wherein an inner water-in-oil (w/o) emulsion is stabilized by dispersing in a solvent-saturated aqueous phase containing an emulsion stabilizer. A ternary w/o/w emulsion is then formed by emulsifying the above w/o emulsions in an external precooled aqueous phase containing an o/w emulsifier. Essentially, the inner w/o emulsion is comprised of an aqueous layer containing from ~2 to about 20% (w/w) of the active agent to be entrapped and an oil layer containing poly (lactide/glycolide) copolymer in concentrations ranging from ~5 to about—50% (w/w oil phase). The copolymer includes molecular weight ranging from 2,000 to about 60,000 daltons, with molar composition of lactide/glycolide from 90/10 to 40/60 and a blend of its uncapped and end-capped forms in a ratio of 100/0 to 1/99. Very high encapsulation efficiencies of about 80 to 100% are achieved depending on polymer molecular weight and structural form.

Programmable release of active core over variable durations between 1–100 days is achieved by a judicious selection of process parameters such as polymer concentration, peptide concentration and the aqueous/oil phase ratio.

This invention is particularly suitable for high encapsulation efficiencies and burst-free, continuous programmable release of polypeptides of molecular weights ranging from 1,000 to about 250,000 daltons, and also other biologically active agents over a period of 1–100 days. A uniqueness of the invention is that when using a 100/0 blend of the uncapped and capped polymer, the final phase of active core release is concurrent with the complete solubilization of the polymer to innocuous components, such as lactic and glycolic acids. This is a significant advantage over the currently available 30 day—release systems wherein a major regulatory concern is about toxicity of residual polymer at the site of administration, long after release of the active core.

The microcapsules described in this invention are suitable for administration via several routes such as parenteral (intramuscular, subcutaneous), oral, topical, nasal, rectal and vaginal routes.

BRIEF DESCRIPTION OF DRAWINGS

FIG. **1** shows a comparison of drug release from a conventional system versus a controlled release system. Peak and valley levels from conventional administrations are shown, in contrast to the steady therapeutic levels from the controlled release administration.

FIG. **2** shows a scanning electron micrograph of PLGA microspheres prepared by the process described in the